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A STUDY OF CARBOHYDRATE METABOLISM IN SCLERODERMA*

PRELIMINARY REPORT

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Scleroderma is a well recognized clinical entity which has been known to the physician for more than 200 years. This mesenchymal disorder has been the subject of numerous clinical, pathological and biochemical investigations, yet its pathogenesis remain entirely unknown.

During the past 2 years we studied several kidney biopsies from scleroderma patients by means of light microscopy with the periodic acid-Schiff stain (PAS). None of these patients had significant impairment of kidney function except for a few who had a mild reduction in the glomerular filtration rate. The most striking histological findings were a diffuse or focal increase in the width of the basement membrane of the glomeruli, mesangial thickening and hyalinization of arterioles. Since the above findings have been noted in prediabetes and in diabetes mellitus, (1–3) we were prompted to perform glucose tolerance tests (GTT) and plasma immunoreactive insulin (IRI) determinations in patients affected with scleroderma.

MATERIAL AND METHODS

Fifteen cases with systemic and one with localized scleroderma were studied. There were 14 females and 2 males; their ages ranged from 10 to 63 years old. All of the patients with systemic scleroderma had the acrosclerotic type, while the single patient with localized scleroderma had widespread morphea (Case 10). None of these patients had clinical diabetes, except for symptoms of functional hypoglycemia in 3 cases.

The following controls were used: eleven normals, eleven patients with early latent diabetes and 5 with latent (or chemical) diabetes. The normals were individuals of normal weight, negative family history for diabetes and glucose tolerance test with fasting levels below 100 mg%, less than 160 mg% at 1 hour, less than 120 mg% at 2 hours and below 100 mg% at three hours. These criteria for a normal glucose tolerance test are a slight modification of that proposed by Mosenthal and Barry (4) who used an upper limit for the 1st hour of 150 mg%. We define as early latent diabetics obese individuals with normal fasting glucose levels, less than 160 mg% at the 1st hour, less than 120 mg% at the 2nd hour but with functional hypoglycemia, usually noted at the 4th hour of the oral glucose tolerance test (5). We define as latent or chemical diabetics, those patients with the following glucose tolerance curve: normal fasting levels with the 1 hour value exceeding 160 mg% and the 2 hour value above 120 mg%.

All scleroderma patients were ambulatory, and their diets included adequate intake of carbohydrates. There were no symptoms of intestinal malabsorption in this series. None of the patients were on systemic corticosteroids for at least 1 year prior to the time of this investigation. Moreover, none of them were on treatment with drugs known to affect insulin release or glucose metabolism. Following an overnight fast, the first blood sample was drawn by venepuncture. After the ingestion of 100 grams of glucose (50 grams for Case №13 who was 10 years old) blood samples were drawn at half, 1, 2, 3, 4, and 5 hours. Blood sugar was determined with an Auto-analyzer utilizing a modification of Hoffman's method (6). Radio-immuno assay of plasma insulin was done by a modification of the method described by Hales and Randle (7). (Data sheet №5581 of the Radiochemical Center, Amersham, Buckinghamshire, England.)

RESULTS

On the basis of the GTT, the patients were divided into two groups. In Group I the 1st hour reading was above 160 mg% and the 2nd hour above 120 mg%. Ten patients showed this pattern, which is similar to that seen in latent or chemical diabetes. Group II had a 1st hour reading below 160 mg% while the 2nd hour was either above or below 120 mg%. There were six patients in this group of which 2 showed 2nd and 3rd hour levels above 120 mg% while the other 4 had normal or flat curves (see Table I). In the two groups a tendency for hypoglycemia was noted in 8 patients.

The levels and curve distribution of immunoreactive insulin were not uniform but were abnormal in all of the scleroderma pa-

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TABLE I

Blood glucose and plasma insulin concentrations in scleroderma

Case No.	Blood glucose(mg/100 ml)							Plasma insulin (μU/ml)						
	Fasting	½	1	2	3	4	5	Fasting	½	1	2	3	4	5
	hours							*hours*						
Group I														
1	96	153	196	201	152	62	54	31	237	410	790	700	175	80*
2	98	169	162	150	140	86	76	25	62	68	52	44	28	42
3	98	180	211	153	154	96	61	10	74	100	185	235	110	72
4	86	154	222	189	155	69	67	105	275	650	540	370	155	112
5	84	164	202	242	69	59	84	12	202	87	560	92	25	14
6	85	150	166	199	100	97	58	25	64	240	130	115	54	26
7	105	197	199	186	129	76	66	37	71	69	147	115	22	32
8	91	131	163	131	123	109	67	21	66	65	117	125	54	10
9	100	175	231	170	56	69	84	16	17	210	300	35	23	14
10	75	111	165	153	107	93	51	16	44	100	110	75	59	18
Group II														
11	94	149	147	131	125	92	84	13	96	110	99	39	76	10
12	75	152	126	161	124	96	52	10	185	360	347	212	82	61
13	114	138	112	91	101	94	100	23	130	295	145	190	120	122
14	101	111	102	79	102	68	95	27	69	115	99	86	27	10
15	91	138	141	106	100	81	84	29	57	135	—	109	28	28
16	86	130	131	100	120	113	118	53	52	67	49	63	56	86

* This determination was performed at 4:05 hours because of hypoglycemic shock.

TABLE II

Blood glucose and plasma insulin concentrations during oral glucose tolerance test

	Blood glucose (mg 100 ml)							Plasma insulin (μU ml)						
	Fasting	½	1	2	3	4	5	Fasting	½	1	2	3	4	5
	hours							*hours*						
Scleroderma														
Group I (10)	92 ± 3*	158 ± 7	192 ± 8	177 ± 10	119 ± 11	82 ± 5	67 ± 4	30 ± 8	111 ± 27	200 ± 58	293 ± 75	191 ± 62	71 ± 17	42 ± 10
Group II (6)	94 ± 5	136 ± 6	127 ± 6	111 ± 11	112 ± 5	91 ± 6	89 ± 8	26 ± 6	98 ± 19	180 ± 44	148 ± 47	117 ± 26	65 ± 13	53 ± 17
Normal (11)	86 ± 1	124 ± 3	138 ± 1	98 ± 1	87 ± 0.6	88 ± 1	86 ± 0.4	19 ± 1	97 ± 3	90 ± 4	54 ± 2	42 ± 2	20 ± 1	16 ± 1
Early latent diabetes (11)	88 ± 1	119 ± 2	143 ± 2	95 ± 2	89 ± 1	41 ± 2	76 ± 1	33 ± 2	69 ± 2	127 ± 5	143 ± 6	152 ± 5	172 ± 12	128 ± 7
Latent diabetes (5)	89 ± 2	147 ± 3	168 ± 2	135 ± 3	124 ± 2	87 ± 4	94 ± 6	38 ± 8	44 ± 10	112 ± 16	134 ± 25	148 ± 23	130 ± 27	72 ± 20

* Mean and SEM.

Figure in parentheses indicates the number of patients.

tients included in this series. In Group I six patients showed hyperinsulinism with the peak usually taking place during the 1st or 2nd hour following the oral glucose load (Cases 1, 3, 4, 5 6, 9). Three patients (Cases 7, 8, 10) showed a lower concentration of insulin, although the curve was of a delayed type. Only Case #2 showed a low and flat curve although, at the 5th hour the insulin levels were still above those of the fasting sample. In Group II, two cases

showed hyperinsulinism (Cases 12, 13) while the others revealed a delayed curve.

Normals showed the peak of insulin activity at half an hour, followed by about a 50% reduction by the 2nd and 3rd hour, and returning to about fasting levels by the 4th to 5th hour. The early latent and latent diabetics showed a delayed insulin response, with the peak of activity at the 3rd-4th hour and remaining above fasting levels at the 5th hour (see Table II).

COMMENTS

This study revealed a high incidence of abnormal GTT in scleroderma. The IRI showed hyperinsulinism and or a delayed type of curve pattern.

There was no correlation between the insulin curves and the presence of obesity. In this series only 2 patients could be classified as obese (Cases 1, 15), two were underweight (Cases 5 and 13) while the other 12 had weights within normal limits. This is particularly noteworthy in view of recent reports suggesting that obesity and not diabetes mellitus itself is responsible for insulin hypersecretory responsiveness (8, 9).

Since the basic defect in diabetes mellitus is not known, it is , at present, impossible to ascertain whether the carbohydrate abnormality in scleroderma represents genetically determined diabetes or whether it belongs to the group of secondary hyperglycemias such is seen in acromegaly, liver cirrhosis, pancreatitis, etc. In this regard there were six patients with a positive family history of diabetes in Group I and two in Group II. Further one may raise the question as to whether kidney involvement in scleroderma may be related to the presence of latent diabetes.

The possible relationship between a carbohydrate abnormality and the connective tissue alterations observed in scleroderma is open for speculation. In this regard, one of us (RF) recently reported an increase in collagen bound hexosamines in the dermis from scleroderma patients (10). The hypothesis that collagen may chemically interact with some carbohydrates was demonstrated in a recent study in which chemical analysis of a purified hyaline revealed it to consist of collagen with a significant increase in bound hexoses and hexosamines (11).

We believe that the possible relationship between abnormalities in carbohydrate metabolism and connective tissue pathology should be investigated in scleroderma as well as in diabetes mellitus.

SUMMARY

Blood glucose and plasma immunoreactive insulin levels were measured during a 5 hour oral glucose tolerance test in a series of sixteen patients with scleroderma. Normals, early latent and latent or chemical diabetics were used as controls. There was a high incidence of abnormal glucose tolerance tests in scleroderma patients with a pattern similar to that seen in latent or chemical diabetes mellitus. Immunoreactive insulin levels revealed an increased output and or a delayed type of response. The possible implications between carbohydrate metabolic derangements and connective tissue pathology are discussed.

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